PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Rajindra Aneja	§	Group Art Unit: 1626
Serial No.: Unknown	§	
Filed: January 24, 2002	§	Examiner: Ambrose, M.G.
Prior Serial No.: 09/292,242	§	
Prior Filing Date: April 15, 1999	§	Atty. Dkt.: 4020.000582
For: LABELLED PHOSPHOINOSITIDES AND ANALOGUES	§	

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Kathy Danas

Kathy Danas

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination on the merits, the Examiner is respectfully requested to enter the following amendments. Remarks supporting patentability of all claims are also included, which the Examiner is respectfully requested to consider. All claims are believed to be condition for allowance, and examination and consideration is respectfully requested on this basis.

AMENDMENT

In the Specification:

Please replace the entire specification from the parent application, other than the claims, with the enclosed substitute specification.

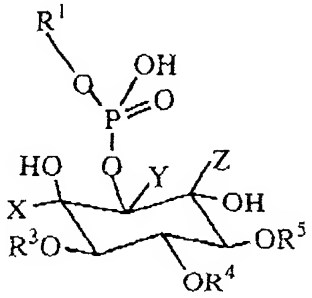
In the Claims:

The accompanying paper requests cancellation of all pending claims except claim 1, without prejudice or disclaimer.

Please further cancel claim 1, after according a filing date to this application.

Please add new claims 21-54, as follows:

21. A substantially purified sphingo-phosphoinositol analogue of a phosphoinositide compound that comprises at least a first stable or radioactive isotope label within the inositol, ceramide or sphingosine residue of said phosphoinositide compound; wherein said stable or radioactive isotope label is selected from the group consisting of ^{2}H, ^{3}H, ^{32}P, ^{33}P and ^{35}S and wherein said phosphoinositide compound has the *myo*-inositol-based structure:



wherein:

R^1 = Ceramide residue or derivative thereof, or Sphingosine residue or derivative thereof;

R^3, R^4, R^5 = H or $Q(T)(OH)_2$;

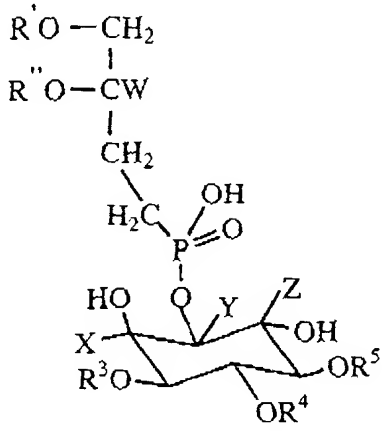
Q = P, ^{32}P or ^{33}P;

T = O, S or ^{35}S;

W, X, Y, Z = ^2H, ^3H or H; and

wherein said structure contains at least one ^2H, ^3H, ^{32}P, ^{33}P or ^{35}S as isotopic label.

22. A substantially purified C-phosphonate analogue of a phosphoinositide compound that comprises at least a first stable or radioactive isotope label within the inositol or the C-phosphonate-phosphatidyl residue of said phosphoinositide compound; wherein said stable or radioactive isotope label is selected from the group consisting of ^2H, ^3H, ^{32}P, ^{33}P and ^{35}S and wherein said phosphoinositide compound has the *myo*-inositol-based structure:



wherein:

R', R" = fattyacyl, alkyl or H;

R^3, R^4, R^5 = H or $Q(T)(OH)_2$;

Q = P, ^{32}P or ^{33}P;

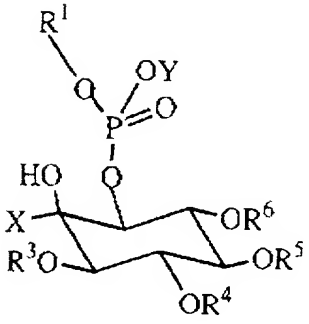
T = O, S or ^{35}S;

W, X, Y, Z = ^2H, ^3H or H; and

wherein said structure contains at least one ^2H, ^3H, ^{32}P, ^{33}P or ^{35}S as isotopic label.

23. The C-phosphonate phosphoinositide compound of claim 22, wherein said phosphoinositide compound comprises at least a first (poly)unsaturated fattyacyl residue.

24. A synthetic intermediate of an isotopically labelled sphingo-phosphoinositol analogue of a phosphoinositide compound, said synthetic intermediate comprising temporary protecting groups at hydroxyl, nitrogen and phosphate positions other than the position into which the isotopic label is to be introduced; wherein said synthetic intermediate has one of the *myo*-inositol-based structures:



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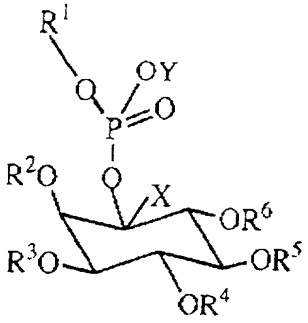

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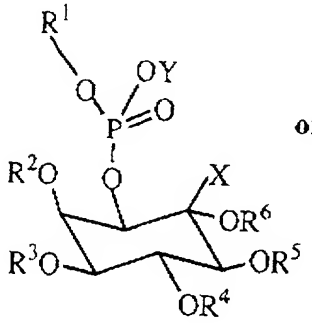

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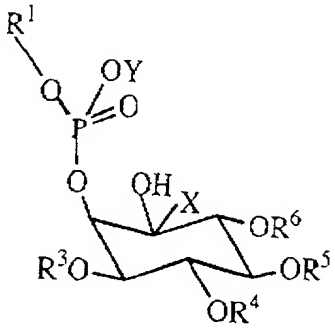
or



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wherein:

X = H, ^{2}H or ^{3}H; Y = alkyl, CH_3, H or (O protecting group);

R^1 = Ceramide residue or derivative thereof, or Sphingosine residue or derivative thereof;

R^3, R^4, R^5 = (OH protecting group), (Q(T)(O protecting group)$_2$), (Q(T)(OH)(O protecting group) or (Q(T)(OH)$_2$);

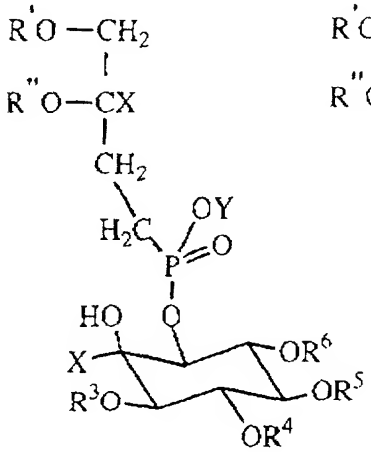
R^2, R^6 = H or (OH protecting group);

Q = P, ^{32}P or ^{33}P;

T = O, S or ^{35}S; and

wherein said structure contains at least one ^{2}H, ^{3}H, ^{32}P, ^{33}P or ^{35}S as isotopic label.

25. A synthetic intermediate of an isotopically labelled C-phosphonate analogue of a phosphoinositide compound, said synthetic intermediate comprising temporary protecting groups at hydroxyl, phosphonate and phosphate positions other than the position into which the isotopic label is to be introduced; wherein said synthetic intermediate has one of the *myo*-inositol-based structures:



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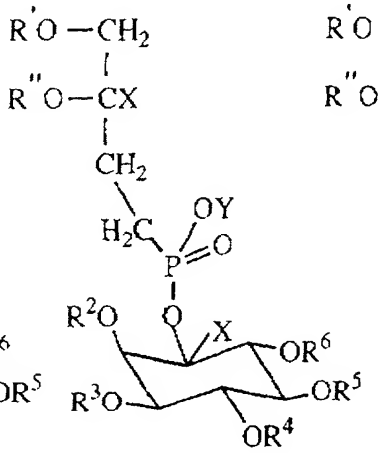

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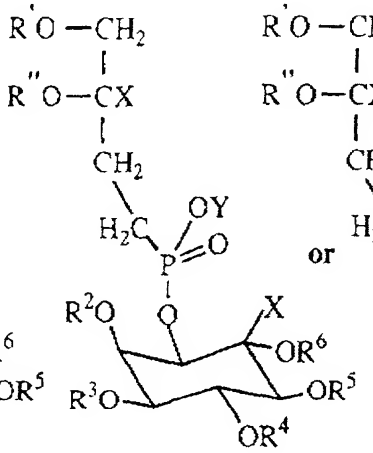

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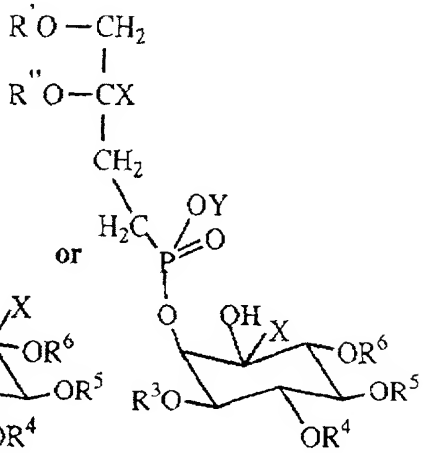

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wherein:

X = H, ^{2}H or ^{3}H; Y = alkyl, CH_3, H or (O protecting group);

R', R" = fattyacyl, alkyl or H;

R^3, R^4, R^5 = (OH protecting group), (Q(T)(O protecting group)$_2$), (Q(T)(OH)(O protecting group) or (Q(T)(OH)$_2$);

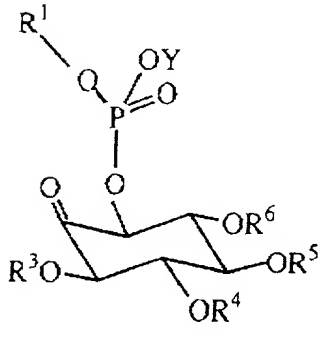
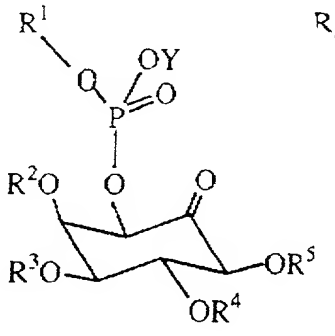
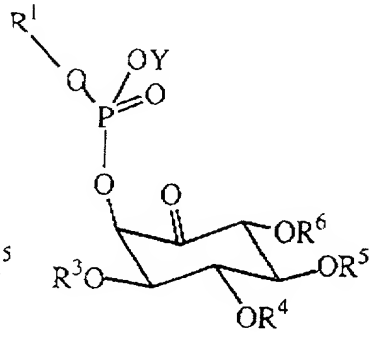
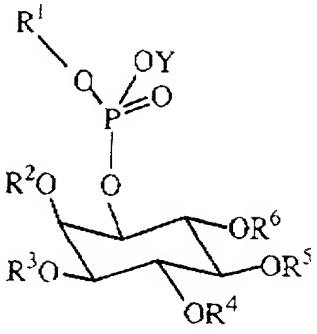
R^2, R^6 = H or (OH protecting group);

Q = P, ^{32}P or ^{33}P;

T = O, S or ^{35}S; and

wherein said structure contains at least one ^{2}H, ^{3}H, ^{32}P, ^{33}P or ^{35}S as isotopic label.

26. A synthetic precursor of a synthetic intermediate of an isotopically labelled sphingo-phosphoinositol analogue of a phosphoinositide compound, wherein said synthetic precursor has a ketone group at the position into which an isotopic ^{2}H or ^{3}H label is to be introduced; wherein said synthetic precursor has one of the structures:

wherein:

Y = alkyl, CH_3 or H;

R^1 = Ceramide residue or derivative thereof, or Sphingosine residue or derivative thereof;

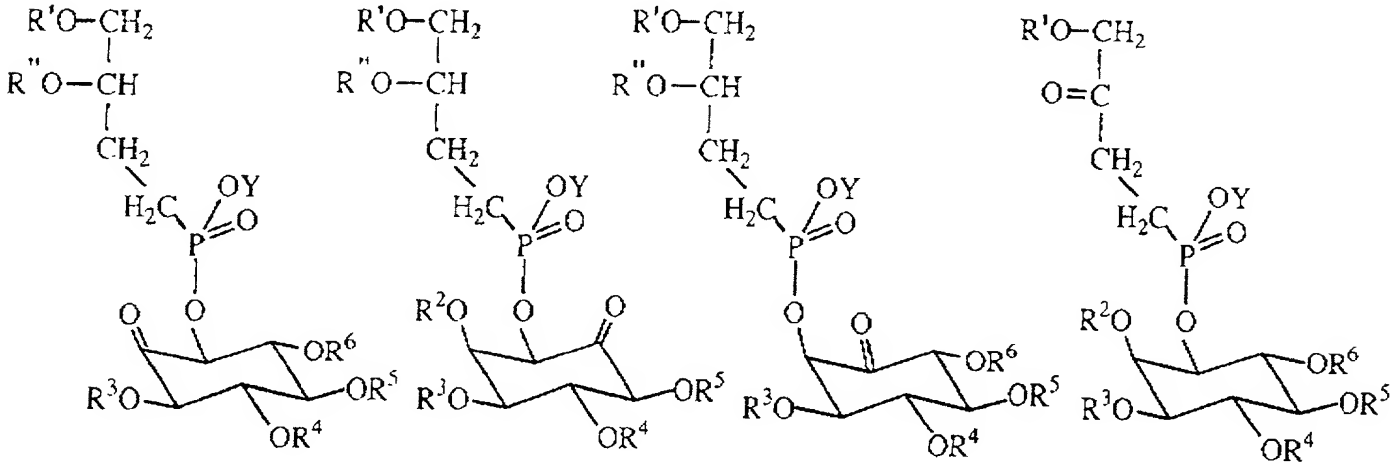
R^3, R^4, R^5 = (OH protecting group), (Q(T)(O protecting group)$_2$), (Q(T)(OH)(O protecting group) or (Q(T)(OH)$_2$);

R^2, R^6 = H or (OH protecting group); and

Q = P, ^{32}P or ^{33}P; and

T = O, S or ^{35}S.

27. A synthetic precursor of a synthetic intermediate of an isotopically labelled C-phosphonate analogue of a phosphoinositide compound, wherein said synthetic precursor has a ketone group at the position into which an isotopic ^2H or ^3H label is to be introduced; wherein said synthetic precursor has one of the structures:



wherein:

Y = alkyl, CH_3 or H;

R', R'' = fattyacyl, alkyl or H;

R^3, R^4, R^5 = (OH protecting group), (Q(T)(O protecting group)$_2$), (Q(T)(OH)(O protecting group) or (Q(T)(OH)$_2$);

R^2, R^6 = H or (OH protecting group); and

Q = P, ^{32}P or ^{33}P; and

T = O, S or ^{35}S.

28. The synthetic intermediate of claim 25, wherein said synthetic intermediate comprises at least a first (poly)unsaturated fattyacyl residue.

29. The synthetic precursor of claim 27, wherein said synthetic precursor comprises at least a first (poly)unsaturated fattyacyl residue.

30. The sphingo-phosphoinositol phosphoinositide compound of claim 21, wherein said phosphoinositide compound further comprises at least a second stable or radioactive isotope label within the ceramide or sphingosine residues of said sphingo-phosphoinositol phosphoinositide compound.

31. The C-phosphonate phosphoinositide compound of claim 22, wherein said phosphoinositide compound further comprises at least a second stable or radioactive isotope label within the alkyl or fattyacyl residues of said C-phosphonate phosphoinositide compound.

32. The sphingo-phosphoinositol phosphoinositide compound of claim 21, wherein said phosphoinositide compound has a structure based on 1D-*myo*-inositol.

33. The sphingo-phosphoinositol phosphoinositide compound of claim 21, wherein said phosphoinositide compound has a structure based on 1L-*myo*-inositol.

34. The C-phosphonate phosphoinositide compound of claim 22, wherein said phosphoinositide compound has a structure based on 1D-*myo*-inositol.

35. The C-phosphonate phosphoinositide compound of claim 22, wherein said phosphoinositide compound has a structure based on 1L-*myo*-inositol.

36. The synthetic intermediate of claim 24, wherein said synthetic intermediate has a structure based on 1D-*myo*-inositol.

37. The synthetic intermediate of claim 24, wherein said synthetic intermediate has a structure based on 1L-*myo*-inositol.

38. The synthetic intermediate of claim 25, wherein said synthetic intermediate has a structure based on 1D-*myo*-inositol.

39. The synthetic intermediate of claim 25, wherein said synthetic intermediate has a structure based on 1L-*myo*-inositol.

40. The synthetic precursor of claim 26, wherein said synthetic precursor has a structure based on 1D-*myo*-inositol.

41. The synthetic precursor of claim 26, wherein said synthetic precursor has a structure based on 1L-*myo*-inositol.

42. The synthetic precursor of claim 27, wherein said synthetic precursor has a structure based on 1D-*myo*-inositol.

43. The synthetic precursor of claim 27, wherein said synthetic precursor has a structure based on 1L-*myo*-inositol.

44. The C-phosphonate phosphoinositide compound of claim 22, wherein said phosphoinositide compound has a structure based on *sn*-glycero-3-phospho as glycerol residue.

45. The C-phosphonate phosphoinositide compound of claim 22, wherein said phosphoinositide compound has a structure based on *sn*-glycero-1-phospho as glycerol residue.

46. The C-phosphonate phosphoinositide compound of claim 22, wherein said phosphoinositide compound has a structure based on *rac*-glycero-3-phospho as glycerol residue.

47. The synthetic intermediate of claim 25, wherein said synthetic intermediate has a structure based on *sn*-glycero-3-phospho as glycerol residue.

48. The synthetic intermediate of claim 25, wherein said synthetic intermediate has a structure based on *sn*-glycero-1-phospho as glycerol residue.

49. The synthetic intermediate of claim 25, wherein said synthetic intermediate has a structure based on *rac*-glycero-3-phospho as glycerol residue.

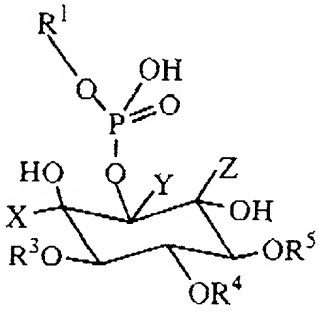
50. The synthetic precursor of claim 27, wherein said synthetic precursor has a structure based on *sn*-glycero-3-phospho as glycerol residue.

51. The synthetic precursor of claim 27, wherein said synthetic precursor has a structure based on *sn*-glycero-1-phospho as glycerol residue.

52. The synthetic precursor of claim 27, wherein said synthetic precursor has a structure based on *rac*-glycero-3-phospho as glycerol residue.

53. A substantially purified sphingo-phosphoinositol phosphoinositide compound that comprises at least a first stable or radioactive isotope label within the inositol, ceramide or sphingosine residue of said phosphoinositide compound; wherein said stable or radioactive

isotope label is selected from the group consisting of ^{2}H, ^{3}H, ^{32}P, ^{33}P and ^{35}S; wherein said phosphoinositide compound has the *myo*-inositol-based structure:



wherein:

R^1 = Ceramide residue or derivative thereof, or Sphingosine residue or derivative thereof;

R^3, R^4, R^5 = H or $Q(T)(OH)_2$;

Q = P, ^{32}P or ^{33}P;

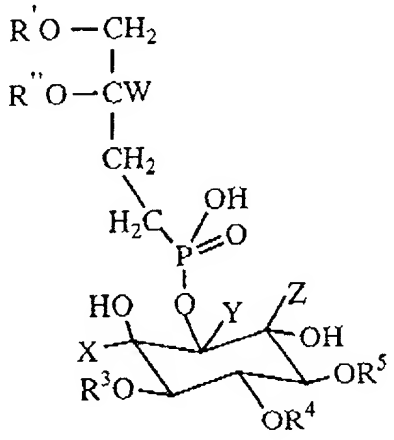
T = O, S or ^{35}S;

W, X, Y, Z = ^{2}H, ^{3}H or H; and

wherein said structure contains at least one ^{2}H, ^{3}H, ^{32}P, ^{33}P or ^{35}S as isotopic label and further comprises temporary protecting groups at hydroxyl and phosphate positions other than the position of at least a first stable or radioactive ^{2}H and ^{3}H isotope label.

54. A substantially purified C-phosphonate phosphoinositide compound that comprises at least a first stable or radioactive isotope label within the inositol or glycerol residue of said

phosphoinositide compound; wherein said stable or radioactive isotope label is selected from the group consisting of ^{2}H, ^{3}H, ^{32}P, ^{33}P and ^{35}S; wherein said phosphoinositide compound has the *myo*-inositol-based structure:



wherein:

R', R" = fattyacyl, alkyl or H;

R^3, R^4, R^5 = H or $Q(T)(OH)_2$;

Q = P, ^{32}P or ^{33}P;

T = O, S or ^{35}S;

W, X, Y, Z = ^{2}H, ^{3}H or H; and

wherein said structure contains at least one ^{2}H, ^{3}H, ^{32}P, ^{33}P or ^{35}S as isotopic label and further comprises temporary protecting groups at hydroxyl and phosphate positions other than the position of at least a first stable or radioactive ^{2}H and ^{3}H isotope label.

REMARKS

I. Divisional Application Status

The present application is a Divisional of allowed, co-pending application Serial No. 09/292,242, filed April 15, 1999 ("the '242 application"; Attorney Docket No. 4020.000500). The inventorship remains the same as the earlier application.

In the response to the first Official Action in the '242 application, Applicant added a number of dependent claims directed to particular embodiments of the claimed invention. These included claims 27, 29 and 30, wherein the glycerolipid moiety is replaced by a ceramide or sphingosine sphingolipid moiety, and claims 31-33, which recited C-phosphonate analogues of phosphatidyl-*myo*-inositols. The Office found each of claims 27, 29, 30 and 31-33 to be drawn to a patentably distinct invention from the original claims and required restriction. The present divisional application is directed to the restricted subject matter.

Applicant respectfully requests that the preceding claims and the enclosed substitute specification be entered prior to substantive examination of this application. All of the amendments in the specification and the additional claims are fully supported by the original parent and earlier provisional applications, to which priority is still properly claimed.

II. Status of the Claims

The accompanying paper requests cancellation of all pending claims except claim 1, without prejudice or disclaimer.

New claims 21-54 have been added, which are fully supported by the original specification. Although the claims are newly presented, each of the claims is directed to subject matter canceled from the claims in the parent application due to a restriction requirement.

Numbering the present claims starting with claim 21 is believed to be correct and claims 21-54 are therefore in the case.

III. Support for the Claims

Claims 21-54 are supported by the original specification and particularly correspond to dependent claims 27, 29, 30 and 31-33, which were pending in the parent application and were canceled in light of a restriction requirement. Certain of these former dependent claims are now presented as independent claims, drafted to reflect the language of the claims allowed in the parent application, but to include the ceramide, sphingosine or C-phosphonate embodiments.

The present claims are first based upon former dependent claims 27, 29 and 30, which represent compounds, intermediates and precursors, respectively, wherein the glycerolipid moiety is replaced by a ceramide or sphingosine sphingolipid moiety. Both ceramide and sphingosine are sphingolipids, and are supported by the specification at least at page 9, lines 9-10. Replacement of the glycerol lipid residue in phosphatidylinositols by either ceramide or sphingosine provides sphingo-phosphoinositol analogues of the phosphoinositides, which are supported in the specification at least at page 9, lines 8-13. The precursor embodiments are supported by the foregoing sections of the specification in combination with pages 14, 15 and 9.

The present claims are next based upon former dependent claims 31-33, and recite C-phosphonate analogues of phosphatidyl-*myo*-inositols. Support for these claims exists at pages 8 and 9 of the specification, with particular reference to page 9, line 11.

The particular correspondence of the current claims with the allowed and restricted dependent claims in the parent application is as follows.

Claim 21 recites a sphingo-phosphoinositol analogue of a phosphoinositide compound, and is based upon allowed claim 1 and former dependent claim 27.

Claim 22 is drawn to a C-phosphonate analogue of a phosphoinositide compound, and is based upon allowed claim 1 and former dependent claim 31.

Dependent claim 23 is based upon allowed claim 2, adapted for the C-phosphonate embodiments.

Current claim 24 recites a synthetic intermediate of the labelled sphingo-phosphoinositol analogue, and is based upon allowed claim 7 and former claim 29. Current claim 25 is drawn to a synthetic intermediate of the labelled C-phosphonate analogue, and is based upon allowed claim 7 and former claim 32.

Present claim 26 is drawn to a synthetic precursor of the synthetic intermediate of the isotopically labelled sphingo-phosphoinositol analogue, and is based upon allowed claim 24, adapted for the sphingo-phosphoinositol embodiments. Present claim 27 recites a synthetic precursor of the synthetic intermediate of the isotopically labelled C-phosphonate analogue, and is also based upon allowed claim 24, but adapted for the C-phosphonate embodiments.

Dependent claims 28 and 29 are based upon allowed claim 2 in the parent case, adapted for the C-phosphonate intermediates and precursors.

Current claims 30 and 31 are drawn to doubly-labelled sphingo-phosphoinositol phosphoinositides or doubly-labelled C-phosphonate phosphoinositides, respectively, and are both based upon allowed claim 28 in the parent case, adapted for the presently claimed compounds.

Dependent claims 32 and 33 are based upon allowed claims 34 and 35, respectively, in the parent application, adapted for sphingo-phosphoinositol phosphoinositides. Current claims 34 and 35 are also respectively based upon allowed claims 34 and 35 from the parent application, adapted for C-phosphonate phosphoinositides.

Present claims 36 and 37 are based upon allowed claims 36 and 37, respectively, in the parent application, adapted for sphingo-phosphoinositol phosphoinositides. Similarly, claims 38 and 39 are based upon allowed claims 36 and 37 from the parent application, adapted for C-phosphonate phosphoinositides.

Current claims 40 and 41 are based upon allowed claims 38 and 39, respectively, in the parent application, adapted for sphingo-phosphoinositol phosphoinositides. Claims 42 and 43 are also based upon allowed claims 38 and 39 from the parent application, adapted for C-phosphonate phosphoinositides.

Dependent claims 44, 45 and 46 are based upon allowed claims 56, 57 and 58, respectively, in the parent application, adapted for C-phosphonate phosphoinositide compounds. Claims 47, 48 and 49 are based upon allowed claims 59, 60 and 61, respectively, in the parent application, adapted for synthetic intermediates of the claimed C-phosphonate phosphoinositide compounds. Likewise, claims 50, 51 and 52 are based upon allowed claims 62, 63 and 64, respectively, in the parent application, adapted for synthetic precursors of the claimed C-phosphonate phosphoinositide compounds.

Independent claim 53 is based upon allowed claim 65 in the parent case, adapted for adapted for sphingo-phosphoinositol phosphoinositides.

Finally, independent claim 54 is based upon allowed claim 65 in the parent application, adapted for adapted for C-phosphonate phosphoinositide embodiments.

It will therefore be understood that no new matter is included within any of the claims in this divisional application.

IV. Compliance with 37 C.F.R. § 1.121

Copies of the pending claims are attached hereto as **Exhibit A**. As the present application is a new application, and as all claims are newly presented without actual amendment of former claims, they are believed to be "original claims" for the purposes of this application. Therefore, it is not believed to be necessary under 37 C.F.R. § 1.121(c) to label each claim "(New)", nor to provide a separate exhibit showing the changes to the claims.

In accordance with 37 C.F.R. § 1.121(b)(3), Applicant elects to enter the amendments to the specification in the form of a substitute specification. This is proper under 37 C.F.R. §§ 1.121(b)(3)(i)(ii)(iii), as the present document contains an instruction to replace specification, along with a first substitute specification in clean form and a second substitute specification, separate from the first substitute specification, marked up to show all changes relative to the previous version of the specification using brackets and underlining.

The minor amendments to the specification are made in order to correct errors of a typographical nature. Each of the amendments were accepted in the '242 application and therefore do not constitute new matter. The precise points of the changes in the substitute specification, made with reference to the text of the '242 application as originally filed, are also detailed in **Exhibit B**.

It will therefore be understood that no new matter is included within the substitute specification submitted as part of the present application.

V. The Claims are Allowable

The parent, '242 application has been allowed and claims will issue that generically cover the claimed invention of phosphoinositide compounds that comprise stable or radioactive isotopes, and synthetic intermediates and precursors thereof. The following reasoning provides

support for the present claims in the context of the parent application, so that the application can be directly progressed to allowance.

The present claims are drawn to sphingo-phosphoinositol and C-phosphonate analogues of phosphoinositide compounds that comprise stable or radioactive isotopes, and synthetic intermediates and precursors thereof. The labelled compounds central to the present application are defined using the same language as allowed in the parent application, supplemented with the ceramide, sphingosine and C-phosphonate features removed from the claims in the parent application in light of the restriction requirement. The correspondence between the allowed claims in the parent application and those of the present application compels a finding of patentability for this divisional application.

For example, the specification relates the presently claimed subject matter to that allowed in the parent case at page 4, lines 25-29, explaining that "the analogues include but are not limited to structural and stereochemical isomers of the cellular phosphoinositides, the corresponding thiophosphates and phosphonates, and the radyl and sphingo type inositolphospholipids. The novel labelled compounds are closely related to the cellular phosphoinositides shown in the generalized structure below".

On page 9, lines 8-13, the specification states: "Further, these methods provide sphingo-phosphoinositol analogues of the phosphoinositides wherein the glycerolipid residue in structure 1 is replaced by ceramide or sphingosine derivatives; other analogues are the corresponding thiophosphates (R^3, R^4 or R^5 = $P(S)(OH)_2$) and phosphonates (a C-P bond in place of O-P in the link to glycerol or inositol). The stereochemical isomers are formed from *sn*-glycero-1′-phospho or *rac*-glycero, and 1L-1(-*myo*-inositol) or DL-1(*myo*-inositol) moieties".

At page 9, lines 15-21, the specification reads: "Labels are located at selected positions in the inositol(phosphate) or the lipid fattyacyl/ alkyl chain(s), glycero or sphingo residues of phosphoinositide analogue structures. Preferably labels are provided as the ^{2}H or ^{3}H isotopes of hydrogen at selected positions, particularly at positions 1, 2 or 6 of the inositol residue (X,Y, Z $=^{1}H$, ^{2}H, or ^{3}H); other label sites are in glycero residue, for instance at the *sn*-glycero-2′- position, and at selected positions along the fattyacyl chains R′ or R′′. Those of ordinary skill in the art would appreciate the chemical structures for such labelled compounds based upon the text, structures and reaction schemes of the present disclosure".

On page 25, lines 19-30, the specification reads: "The synthetic methods disclosed herein are applied also to the 1L- or DL- *myo*-inositol derivatives in addition to the 1D- series shown in Schemes 1 to 5, and each condensed with phosphatidic acid with *sn*-glycero-1- or *rac*-glycero-1/3- configurations in addition to the *sn*-glycero-3- in Scheme 6. Further, various inositol and phosphatidic acids types are cross coupled. Moreover, phosphatidic acids carrying saturated and unsaturated fattyacyl, alkyl, and sphingolipid residues are applied. Thus these methods provide a diversity of structures with the phosphoinositide motif in non-labelled and labelled forms, important labelled precursors of the latter and key intermediates for introducing labels. It is emphasized that the descriptions herein and in the examples are merely illustrative of the invention as defined in the claims. The chemistry and protocols for products with and without isotope labels are identical and hence ordinarily skilled practitioners will understand that synthesis of either type of product is sufficient validation of the novel methodology for both labelled and non-labelled type phosphoinositides".

Further, the description of methods for preparation of the sphingolipid and phosphonate analogues is explicitly recited in the specification, which states: "Moreover, phosphatidic acids

carrying saturated and unsaturated fattyacyl, alkyl, and sphingolipid residues are applied", as quoted above.

Given the allowance of the claims in the parent application, the details in Applicant's disclosure and the technical skill of those of ordinary skill in the art, Applicant submits that the present claims define a patentable invention. Applicant therefore urges that the claims be directly progressed to allowance.

VI. Formalities

The proper claim for priority is timely introduced into the specification by amendment. No drawings are included in the application. Applicant's initial duty of disclosure is met.

A Terminal Disclaimer should not be necessary to secure allowance, as the present application is a proper divisional based upon entry of a restriction requirement in a prior application by the Office. However, should the Office identify concerns that suggest the usefulness of a Terminal Disclaimer, Applicant solicits a telephone call to the Applicant's representative so that the issue can be addressed without delay.

No fees should be due in addition to the enclosed filing fees. However, should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason, the Assistant Commissioner is authorized to deduct said fees from Williams, Morgan & Amerson, P.C. Deposit Account No. 50-0786/4020.000582.

VII. Conclusion

In conclusion, Applicant submits that, in light of the foregoing remarks, the present claims are in condition for allowance and an early indication to this effect is respectfully

requested. Should Examiner Ambrose have any questions or comments, a telephone call to the undersigned Applicant's representative is earnestly solicited.

Respectfully submitted,

Shelley P.M. Fussey
Reg. No. 39,458
Agent for Applicants

WILLIAMS, MORGAN & AMERSON, P.C.
7676 Hillmont, Suite 250
Houston, Texas, 77040
(713) 934-4079

Date: January 24, 2002